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Review

What would Karl Landsteiner do? The ABO blood group and stem cell transplantation

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Summary:

ABO blood group antigens, of great importance in transplantation and transfusion, are present on virtually all cells, as well as in soluble form in plasma and body fluids. Naturally occurring plasma IgM and IgG antibodies against these antigens are ubiquitous. Nonetheless, the ABO blood group system is widely ignored by many transfusion services, except for purposes of red cell transfusion. We implemented a policy of transfusing only ABO identical platelets and red cells in patients undergoing stem cell transplantation or treatment for hematologic malignancies. Major bleeding episodes have occurred in about 5% of patients undergoing induction therapy for acute leukemia as compared with 15–20% in the literature. Overall survival times appear to be superior to that in historical cohorts. In 2002–2004, treatment-related mortality at 100 days in our Blood and Marrow Transplant Unit was 0.7% for autologous transplants ($n = 148$), 13% for sibling allogeneic transplants ($n = 110$), and 24% ($n = 62$) for matched unrelated allogeneic transplants, suggesting that our approach is safe. We speculate that more rigorous efforts on the part of transfusion services to provide ABO identical blood components, and to remove incompatible supernatant plasma, when necessary, might yield reduced morbidity and mortality in patients undergoing stem cell transplantation.

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The ABO blood group system was discovered over a hundred years ago by Karl Landsteiner, a discovery that would ultimately make modern transfusion and transplantation therapies possible. It is one mark of the persistence of long useful, but now inappropriate terms that the concept of ABO 'compatibility,' primarily derived from whole blood and red cell transfusions, is commonly used for organ and stem cell transplants, as well as platelet and plasma transfusions. We will use the terms 'ABO identical or matched,' and 'ABO nonidentical' or 'ABO mismatched,' which more accurately reflect the biology and clinical outcomes of stem cell transplants. So-called ABO 'compatible' transplants or transfusions (eg, an O donor stem cells to an A recipient) invariably contain antibodies (anti-A) to the recipient's antigens, or soluble ABO antigens to which the donor has antibodies (eg, AB fresh frozen plasma to an O recipient). Although little or no attention is paid in traditional approaches to 'compatibility', a group AB fresh frozen plasma transfusion to an O recipient contains soluble A and B antigen that can react with the recipient's anti-A and -B. Thus 'compatibility', which has some clinical meaning for red cell transfusions by predicting the likelihood of hemolysis occurring, does not adequately address issues of clinical complications such as immune complex formation, immunomodulation, transfusion-related acute lung injury (TRALI), or graft-versus-host disease.

Unlike solid organ transplantation of kidneys, livers, and hearts,[1] ABO blood group mismatching between donor and recipient has not been accepted as a significant histocompatibility barrier to stem cell transplantation. What data exist are conflicting, but suggest that differences in ABO blood group between donor and recipient can play a role in graft rejection and overall survival.[2–4] In particular, there are data from observational studies that donors and recipients who are both antigen and antibody nonidentical (eg, a group A transplant to a group B recipient) may have increased treatment-related mortality,[2–4] but further investigation is needed to determine if this is the case. One report, to the contrary, found that ABO nonidentical transplants were actually associated with reduced relapse rates and improved overall survival in patients with acute leukemia.[5] The hypothesized mechanism was more potent graft-versus-leukemia effects in ABO nonidentical transplants.

Increased morbidity after ABO nonidentical transplants has been reported in some series, including mild acute graft-versus-host disease,[3] delayed red cell engraftment and red cell aplasia,[3,6,7] and massive hemolysis.[8] Hemolysis, occasionally life threatening but rarely fatal, is a well-known complication of infusing ABO nonidentical plasma in

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Table 1 Morbidities reported after ABO non-identical transplants and transfusions and hypothesized mechanisms

Graft rejection (uncommon)	Recipient antibody impairs engraftment of ABO mismatched progenitor and stem cells bearing corresponding antigen
Increased treatment-related mortality (? primarily in bidirectional donor antibody and antigen mismatching)	Multiorgan failure due to antibody binding to endothelial and other nonhematopoietic cells; formation of immune complexes
Increased mild acute graft-versus-host disease	Donor cells recognize ABO nonidentical recipient cells as 'foreign'
Delayed red cell engraftment and red cell aplasia	Long half-life circulating recipient anti-A and/or anti-B antibody impairs donor red cell engraftment
Hemolysis	Donor transfused anti-A and/or anti-B, or donor plasma cells from transplant making anti-A/B hemolyse residual recipient nonidentical red cells
Platelet transfusion refractoriness	Only reported in setting of nonleukoreduced transfusions – increased HLA antibody formation, ABO antibodies binding directly to transfused platelets or through an immune complex mechanism
? Increased risk of infection and recurrence of leukemia	Immune complex mediated type 2 immune deviation and impaired phagocyte/macrophage function

platelet concentrates, fresh frozen plasma, or even red blood cell concentrates[9,10] (Table 1).

Why a major side mismatched stem cell transplant, ABO nonidentical donor given to a recipient who possesses the corresponding antibody (eg, an A donor to an O recipient) does not yield acute rejection or treatment-related mortality as seen in similar kidney, liver, and heart transplants is largely unknown. Even after myeloablative conditioning regimens, employed in stem cell but not solid organ transplants, circulating anti-A antibody persists for weeks or months in group O recipients. There is no doubt that mature platelets, red cells, and white cells express group A and B antigens, but perhaps stem cells and progenitor cells do not possess or possess much lesser amounts of antigen. Little is known about the blood group antigens present on hematopoietic or lymphoid stem and progenitor cells.

The absence of markedly increased graft rejection or treatment-related mortality due to ABO nonidentical stem cell transplants is particularly mystifying given that ABO nonidentical transfusions of mature peripheral blood cells such as red cells, platelets, and granulocytes are frequently accompanied by acute hemolysis and other transfusion-related morbidity. Red cell transfusions that are minor side mismatched, with the donor having antibody to a recipient antigen (eg, an O red cell transfusion to a non-O recipient), are used in emergencies as 'universal donors.' These transfusions have a reasonable risk to benefit ratio when used in life-threatening hemorrhagic emergencies, despite the ever present small risk of severe hemolytic reactions.

Most modern red cell preparations contain only a few dozen milliliters of plasma, as compared with several hundred milliliters of plasma in a transfused platelet concentrate or unit of fresh frozen plasma. ABO nonidentical red cells are infrequently given, and major side mismatched ABO red cells (eg, an A red cell transfused to an O recipient) are never intentionally transfused. Nonetheless, ABO nonidentical platelets remain an acceptable choice in most centers for transfusions to patients undergoing stem cell transplants. In patients undergoing stem cell transplants from ABO nonidentical donors, it is virtually impossible to choose conventionally prepared red cell and platelet products that do not contain ABO antigen and/or antibody that are mismatched with either the donor or recipient.

What, if any, are the consequences of these transfusions of ABO nonidentical platelet and red cell concentrates to the stem cell transplant patient? There are few data to support the safety and efficacy of current practices.[11] What data exist primarily come instead from the setting of randomized trials in patients undergoing induction therapy for acute leukemia, and some observational studies in stem cell transplantation. Most of these studies do not follow patients longitudinally through consolidation and transplant therapy to determine if transfusion practices alter clinical outcomes. Do the existing findings in predominately adult patients apply to children undergoing stem cell transplantation? Do the results in patients with leukemia extrapolate well to patients with other diagnoses? Little to no data exist to answer these questions (Table 2).

Table 2 Limitations of studies of ABO nonidentical transplants and transfusions

Stem cell transplantation

No randomized controlled trials of ABO identical *vs* nonidentical donors as the graft source, nor the relative importance of ABO *vs* minor HLA mismatching

Studies do not differentiate between identical and nonidentical transplants, but employ various red cell transfusion-based definitions of 'compatibility' that may not be applicable to stem cell transplants

Transfusion studies

Randomized trials involve induction therapy for acute leukemia in adults, but not stem cell transplantation or other diseases or pediatrics

Randomized trials of ABO mismatching employed nonleukoreduced transfusions

ABO and platelet transfusion refractoriness

For many years the most common, troublesome, and serious acute complication of platelet transfusion therapy was refractoriness.[12] Refractoriness typically occurred in patients with prior pregnancies or repeated platelet transfusions. It was not uncommon for a patient to become transfusion refractory within the first few transfusions during induction therapy for acute myeloid leukemia in adults. Half or more of the patients eventually failed to achieve clinically satisfactory increments with transfusions.[13] Many patients at the nadir of chemotherapy-induced thrombocytopenia had counts of under 5000/μl and no increments after transfusion of multiple doses of platelets. Some experienced life threatening or fatal bleeding, and often it was not clear whether transfusing

platelets in the face of no increments did more harm than good.

HLA-matched platelets overcame this problem in slightly more than half of refractory patients, fairly dismal contrasted with the 95–100% success of antigen negative red cell transfusions to alloimmunized patients. Given the frequency of HLA alloimmunization in refractory patients and the data suggesting that donor white cells were the stimulus for alloimmunization rather than the platelets themselves, white cell reduction filters were developed by a number of companies. Leukoreduction was rapidly shown to reduce the incidence of both alloimmunization and platelet transfusion refractoriness in randomized trials,[14] culminating in a particularly large and convincing trial, the TRAP study.[15]

Two randomized trials from the era before leukoreduction of platelet transfusions demonstrated that administering solely ABO identical platelets reduced the rate of HLA alloimmunization, and of platelet transfusion refractoriness in patients with leukemia receiving repeated transfusions.[16,17] The post transfusion platelet counts were higher, the number of platelet transfusions required in the early part of the patient's clinical course was almost halved, pre-existing HLA antibody titers did not increase, and the onset of refractoriness was delayed compared with patients receiving ABO nonidentical platelets. In our studies, transfusion of group O platelets to non-group O recipients appeared to be most detrimental to post transfusion platelet increments, suggesting that the nonidentical plasma was a major contributing factor.[17,18] These latter data replicated those from a third study.[19]

The rate of refractoriness was decreased five-fold when ABO identical platelets were given instead of platelets bearing ABO antigens to which the recipient had antibody,[16] and was reduced two-fold when ABO identical platelets were given instead of randomly selected nonidentical platelets.[17] The deleterious effect of ABO mismatching is cumulative with increasing transfusion number. Thus patients likely to receive many transfusions will particularly benefit from receiving ABO identical platelets.[18] There is a potential favorable effect of ABO identical platelet transfusions on survival in acute leukemia[20] and survival after cardiac surgery,[21] but these studies are small and observational. Are ABO identical platelet transfusions still required to prevent platelet refractoriness in the post-leukoreduction era? No clear cut data exist, but we believe there is evidence in favor of administering ABO identical platelets even after introduction of leukoreduction of transfusions. Our current policy, when time allows, is to use washed group O red cells and platelets as universal donor transfusions when ABO identical red cells and platelets are not available.

ABO nonidentical platelet transfusions during remission induction therapy for acute leukemia are associated with treatment-related morbidity/mortality

In trials of prophylactic platelet transfusions approximately 15–20% of patients with newly diagnosed acute leukemia have major bleeding episodes (WHO grade II and higher).[22] Typical major bleeding rates during myeloablative stem cell allotransplantation are even higher at approximately 25%.[23] Autologous transplant bleeding rates are in the range of 6%.[23] It is not known whether bleeding in allogeneic stem cell transplant recipients is correlated with ABO mismatching of donor and recipient, but this would be worth investigating.

In our patients with acute leukemia transfused solely with ABO identical platelet transfusions, the prevalence of major bleeding has been less than 5%, or 2–4-fold lower than reported in the literature.[24] More than 70% of patients in our recently reported randomized trial had no clinically evident bleeding of any sort ($n=43$ patients). It seems plausible that infusion of nonidentical ABO antigen and antibody, subsequent binding of antibody to platelets and endothelial cells, or formation of immune complexes might contribute to bleeding through interference with inflammatory and/or hemostatic function. There are theoretical reasons to hypothesize that infusing large amounts of ABO mismatched antigen or antibody, and the ensuing creation of high molecular weight immune complexes of ABO antibody and soluble ABO antigen could have deleterious effects on immunologic and hemostatic functions.[25]

Life-threatening hemolytic anemia can occur with infusion of ABO nonidentical plasma in platelet transfusions.[9,10] Our practice is to identify patients who will need repeated transfusions of platelets and administer only leukoreduced, ABO identical platelets to these patients. If ABO identical platelets are not available, we make an effort to provide plasma-depleted ABO antigen 'compatible' platelets such as washed group O platelet concentrates. In patients requiring only single platelet transfusions we attempt to give ABO identical, but when none are available in urgent situations, we give the least dangerous ABO mismatch that is on hand. For example, group A and B platelets are probably safer for a group AB recipient than group O platelets due to the absence of high titer anti-A, B. The only future route to the ideal goal of ABO identical platelets for all patients is to either manufacture many more platelets than are needed (with increased outdating and cost), or to extend the storage period for platelets so that larger inventories can be maintained, as with red cells (Table 3).

It is our opinion that all patients with hematologic diseases or undergoing stem cell transplantation receiving

Table 3 Suggested approach to transfusion therapy in stem cell transplant recipients and other patients receiving multiple transfusions

Transfuse only leukoreduced blood components
Transfuse only ABO identical blood components
When this is not possible because of ABO nonidentical transplants, or shortages of ABO blood group identical components
Use red cell and platelet transfusions lacking soluble ABO antigen to which the recipient has antibody (usually group O red cells and platelets)
Remove supernatant plasma containing antibody to recipient or donor ABO antigens before transfusion, by washing or centrifugation
Except when serious shortages occur, do not transfuse ABO nonidentical components merely for purposes of blood bank inventory control (ie, to prevent wastage)

platelet transfusions should receive leukocyte-reduced platelets to avoid HLA alloimmunization and transfusion refractoriness. This is the standard of practice in almost all centers and is cost effective and perhaps even cost saving.[26] In addition to reducing HLA alloimmunization, use of leukoreduction filters appears to lower the risk of alloimmunization to red cell antigens,[27] presumably through an indirect immunologic mechanism.

The use of HLA-matched platelets has dropped precipitously in our hospital since the introduction of leukoreduction and use of ABO identical platelets for patients receiving multiple transfusions in 1990. Use of HLA matched platelets peaked in 1989 at 15% of all platelets transfused prior to instituting leukoreduction and use of ABO identical platelets. In recent years, HLA matched platelets constitute about 1% of the 20 000 + units of platelets transfused. Platelet transfusion refractoriness, which formerly affected 50% or more of patients with acute leukemia, now affects fewer than 5% of these patients. While still a difficult problem in specific patients, it is much smaller in scope.

In reviewing a database of 118 patients treated with full-dose induction therapy for adult acute leukemia in our institution during 1985–1995, the number of days with clinically evident bleeding during the initial admission has dropped substantially since the introduction of leukoreduced, ABO identical transfusions (Figure 1). As these two measures were introduced simultaneously, it is impossible to sort out the relative roles in this improvement.

Likewise, overall survival has improved, but this result is confounded with improvements in post-remission therapies such as consolidation and transplantation, and other supportive measures (see Figure 2). Nonetheless, we speculate that introduction of an ABO identical transfusions only policy may have contributed in some degree to these improved outcomes, given the survival advantage with ABO identical platelet transfusions seen in an earlier small randomized trial.[20]

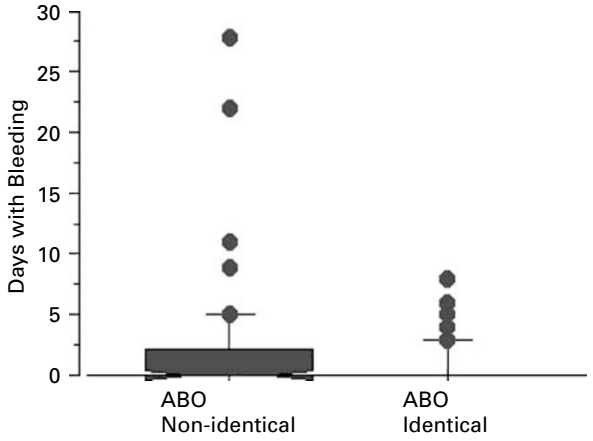

Figure 1 A box plot of number of days with bleeding on the ordinate is shown for 46 adult patients with acute leukemia undergoing induction therapy receiving ABO nonidentical platelet transfusions *vs* 67 receiving ABO identical platelet transfusions during 1985–1995 (five patients had missing data). The mean number of days with bleeding of any sort in the group receiving ABO nonidentical platelet transfusions was 2.3 ± 5.5 (1 s.d.) as compared with 0.75 ± 1.7 in the ABO identical group ($P = 0.034$ by unpaired t test).

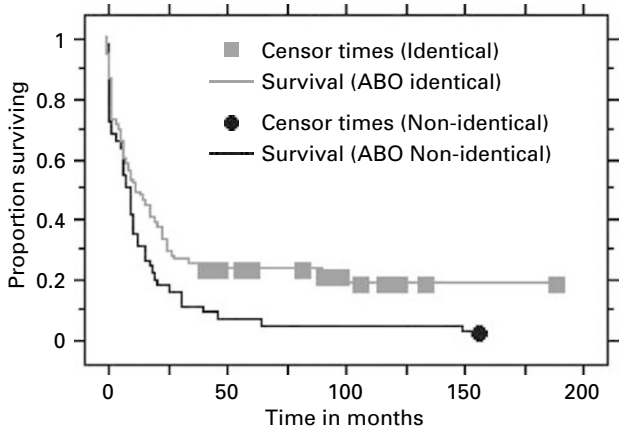

Figure 2 Survival in adult patients with acute leukemia undergoing full-dose remission induction chemotherapy receiving either ABO identical ($n = 72$) or nonidentical platelet ($n = 46$) transfusions during 1985–1995. These curves are statistically significantly different by the log rank test ($P = 0.018$).

ABO, treatment-related morbidity, mortality, and platelet transfusions in stem cell transplantation

As mentioned, previous randomized and observational studies demonstrate that infusion of ABO nonidentical blood components can be associated with platelet refractoriness,[16,17,19] increased titers of HLA-A,B and ABO antibodies,[16] immune complex formation,[28–30] and reduced survival in acute leukemia.[20] Benjamin and co-workers observed increased mortality in ABO nonidentical allogeneic marrow transplant recipients.[31]

Benjamin and Antin later reported that infusion of ABO nonidentical plasma may be associated with an increased incidence of sepsis and multiorgan failure in marrow allograft recipients.[32] After altering their practices to avoid infusion of ABO nonidentical plasma in platelet concentrates, survival differences between recipients of ABO identical and nonidentical allografts were no longer observed. It should be noted that these two sets of observations, while well controlled, were observational and subject to bias and confounding in a number of ways. These observations by Benjamin and Antin regarding unfavorable clinical outcomes after ABO nonidentical platelet transfusions in stem cell transplant patients parallel those seen after allogeneic transfusions in the surgical setting.[33]

Surgical patients receiving allogeneic transfusions develop impaired cellular immunity[34–38] associated with increases in postoperative bacterial infections,[39–42] cancer recurrence,[43,44] multiorgan failure,[45–50] and poorer wound healing.[51–53] Could ABO nonidentical transfusions cause impaired cellular immune function, infection, and multiorgan failure, but by a different mechanism than that causing hemolysis?

It has been documented that infusion of nonidentical ABO antibody or antigen leads to the accumulation of

immune complexes in the recipient's peripheral blood.[29] For some time it has been known that immune complexes can impair cellular immunity by suppressing macrophage activation in response to pathogens.[54] This effect appears to be mediated at least in part by IL10.[55] Furthermore, neutrophil apoptosis is significantly increased in the presence of antibody-coated red blood cells.[56] The presence of immune complexes impairs secretion of IL12.[57] These changes resemble the shift toward a type 2 (Th2) pattern of cytokine secretion and downregulation of NK, T, and macrophage cellular immunity seen after allogeneic transfusion in the surgical setting.[33,36,38,58,59] Infusion of nonidentical ABO antibodies and antigens might be expected, speculatively, to cause type 2 immune deviation and downregulate host cellular defenses against both infection and malignancy. Earlier work suggests that high levels of immune complexes, both prior to induction therapy and while in remission, predict poorer outcome in acute myeloid leukemia.[60]

The infusion of ABO nonidentical platelets or plasma to patients produces complex immunological effects, and has been associated with poorer clinical outcomes in the setting of leukemia treatment as well as in the stem cell transplant setting. Patients receiving ABO nonidentical platelets develop increased blood levels of immune complexes consisting of ABO antigens and their corresponding antibodies.[29] These complexes circulate for hours to days after the nonidentical transfusion and can activate complement and may contribute to the development of refractoriness in some patients.[17,19,28–30] The detrimental effects of repeated transfusions of ABO-mismatched plasma also are cumulative.[18] Platelets (and most white cells) carry an Fcγ receptor as well as complement receptors for C1q. Exposure of platelets to C1q multimers or immobilized C1q at concentrations similar to those seen in refractory hematological patients result in platelet activation, and once activated the platelets are rapidly cleared from the circulation.[61,62] In addition, normal platelets after being exposed to monomeric IgG anti-A or to immune complexes containing IgG anti-A become more adherent to phagocytic monocytes *in vitro*.[28]

We examined the small number of adult patients with acute leukemia in our institution managed with either ABO nonidentical or ABO identical platelet transfusions throughout their care, restricted to those who achieved complete remission and underwent stem cell transplantation during 1985–1995. An even larger survival advantage was found than for the cohort as a whole but because the number of patients is quite small, this result is not statistically significant (Figure 3). In addition, because this is observational, longitudinal data, the potential for confounding and bias exist. Thus, these observations are intriguing clues to a role for ABO nonidentical transfusions as a cause of morbidity and mortality in stem cell transplantation, but remain purely speculative without further data.

Treatment-related mortality in our institution has been quite low, and it may be that to some undetermined extent this is related to our choice to avoid ABO nonidentical transfusions. Treatment-related mortality in 2002–2004 in our stem cell transplant unit at 100 days has been 0.7% for

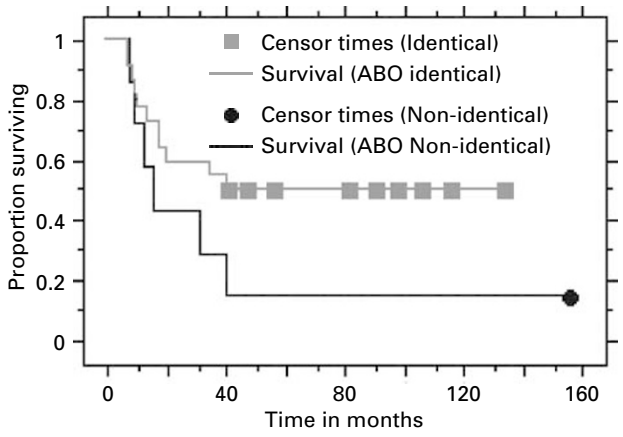

Figure 3 Survival in adult patients with acute leukemia undergoing full-dose remission induction chemotherapy, achieving complete remission and then undergoing bone marrow transplantation, receiving either ABO identical ($n=22$) or nonidentical platelet ($n=7$) transfusions during 1985–1995. These curves are not quite statistically significantly different by the log rank test ($P=0.11$).

autologous transplants (four of 148), 13% for related allogeneic donor transplants (14 of 110), and 24% for matched unrelated allogeneic transplants (15 of 62). Obviously, diagnosis mix, degree of myeloablation, remission status, and many other factors play the major role in whether these results are considered excellent, average, or otherwise. For reference, in 2000 through 2004, 40 of 92 stem cell transplants for adult acute leukemia were in patients not in complete remission, and 52 of 61 transplants for diffuse large cell non-Hodgkin's lymphoma were in patients with relapsed or advanced disease. Thus, these favorable treatment-related mortality results derive from a relatively high-risk population. Whether avoidance of ABO nonidentical transfusions plays any role in these results is once again speculative. Mortality data are influenced by so many factors that it will be difficult of ascertain what role, if any, ABO identical transfusions play in these results.

One additional concern is that pulmonary failure is a common complication of stem cell transplantation. It is now accepted that transfusion-related acute lung injury (TRALI) is caused by combined effects of transfused mediators, such as antibodies and cytokines present in the transfused blood (particularly platelet transfusions in some series) as well inflammatory or other immunologic effects of the patient's underlying illness.[63] Recent evidence suggests that immune complexes could play a role in the development of acute lung failure.[64] Given that transfusion of ABO nonidentical platelets generates large amounts of long-lived, high molecular weight immune complexes,[29] we hypothesize that ABO nonidentical transfusions may be a previously unrecognized contributing cause of TRALI and similar pulmonary dysfunction syndromes in stem cell transplant patients.

Commentary

The terminology 'ABO compatible' that is employed in transfusion medicine has added to the confusion in

thinking about this subject.[18] If we wish to address antigen–antibody interactions in solution (ie, formation of ABO immune complexes) as well as at the cell-plasma interface (hemolysis), the term 'compatible' becomes problematic, and perhaps misleading. The term ABO 'compatible' comes solely from the extensive clinical experience with red cell transfusions. Although dangerous group O universal donors with potent ABO agglutinins are well described, group O red cell concentrates usually can be safely transfused to non-group O patients because the amount of residual incompatible plasma is minimal. Whether events other than hemolysis are occurring with ABO nonidentical transfusions with small amounts of plasma is unknown and unstudied.

In contrast to red cells, apheresis and whole blood platelet concentrates are suspended in several hundred milliliters of donor plasma. If 5 units of platelet concentrate are transfused to a patient, a quarter of a liter of plasma will be infused. If these platelets are ABO nonidentical, large volumes of mismatched plasma are transfused, often on a daily basis for extended periods of time. Blood components contain both cells carrying the ABO antigens of the donor and plasma containing both ABO antibodies and soluble ABO antigens borne by glycolipids and glycoproteins. The recipient also possesses ABO antigens and antibodies but in much larger amounts. In group O products, cellular and soluble A and B antigens are absent but anti-A and anti-B may be present in higher titer and avidity than in the other ABO blood types. ABO antigens are also ubiquitously present on other tissue cells and in secretions.

Thus, unlike red cell concentrate transfusions, there are no 'ABO-compatible' platelet or plasma transfusions, but only ABO identical ones.[18] The consequences of infusing ABO nonidentical antibody or antigen in large amounts may not lead to hemolysis, but this does not necessarily mean that repeated infusions of large amounts of nonidentical ABO antigen and antibody are benign. The term 'ABO compatible' for transfusion of plasma containing products and allogeneic transplantation should be abandoned in our opinion until they are proven safe and efficacious. Transfusions and transplants might best be classified as either identical or nonidentical. The nonidentical pairings can be classified as to whether the transfused/transplanted cells or plasma contain nonidentical antigens to which the recipient has antibody, or the transfused plasma contains antibodies to antigens present on the recipient's cells or in their plasma.

What would Landsteiner do and what do we do?

It would be interesting to hear Karl Landsteiner's thoughts on how we should approach the issue of ABO matching and blood transfusions, but he has been beyond communication range for 60 years. However, the ABO system is one the most widely represented antigen systems in the body, and perhaps the most immunologically important overall. It seems likely that Karl Landsteiner would think it prudent to proceed cautiously until the role of ABO is more fully elucidated. Then again, Landsteiner spent almost all of his extraordinarily accomplished and long career as a bench scientist in immunology, and might not care to speculate on a clinical issue. Therefore, failing the ability to consult the originator of the scientific concepts that made blood transfusion and stem cell transplantation possible, we are on our own. At the University of Rochester we have adopted the policy that ABO identical transfusions are the only acceptable ones for patients undergoing stem cell transplantation. Thus we transfuse either ABO type identical red cells and platelets, or remove nonidentical plasma prior to transfusion. We never intentionally transfuse ABO nonidentical cells, for all the obvious reasons (see Table 4). The exceptions are ABO nonidentical stem cell allografts and emergency shortages of ABO identical blood components.

We have taken the approach in allograft recipients transitioning from recipient group A to donor group O of routinely administering washed O red cells and washed O platelets to minimize hemolysis and greatly reduce the formation of immune complexes between recipient A antigen and donor anti-A. Concerns about the effects of plasma depletion and washing on platelet function exist, but we believe there is little reason for worry. In a recent review of close to a thousand consecutive transfusions of washed platelets to about 50 patients, we could find no episodes of even mild clinical bleeding attributable primarily to thrombocytopenia. The only randomized trial addressing the safety of washed platelets demonstrated no increase in clinically serious bleeding in the washed arm of the study, and raised the question of whether overall survival may be superior in patients receiving washed blood components.[24]

Washing or differential centrifugation to remove supernatant plasma is available in many transfusion services, if perhaps not all, that support leukemia and stem cell transplant services. Costs vary, but the disposables, solutions, and technical time are approximately $25–50 (US), not including overhead or any capital expense for a cell washer (eg, Gambro 2991) or apheresis device that is usually present in such transfusion services for purposes of stem cell processing. Methods for washing red cells are widely accepted, and platelet washing techniques

Table 4 Safest transfusions in ABO nonidentical stem cell transplants

Donor	*Recipient*	*Transfused RBC*	*Transfused platelets*	*Transfused plasma/ cryoprecipitate*
O	O	O	O	O
A	A	A	A	A
B	B	B	B	B
AB	AB	AB	AB	AB
O	A, B, AB	Washed O	Washed O	AB
A	O, B	Washed O	Washed O	AB
A	AB	Washed A	Washed A	AB
B	O, A	Washed O	Washed O	AB
B	AB	Washed B	Washed B	AB
AB	O	Washed O	Washed O	AB
AB	A	Washed A	Washed A	AB
AB	B	Washed B	Washed B	AB

employing semiautomated devices are also familiar to most transfusion services in these settings.[65,66] The main obstacle to using washing, leukoreduction, and ABO identical transfusions is increased cost and complexity in the transfusion service. Given that improvements in patient care lead to increased costs in the transfusion service, it is understandable that transfusion service directors are reluctant, if not sometimes resistant to practices that are not universally accepted or mandated by regulation. The benefits in clinical outcomes and reduced costs of care are experienced by the patient, the hospital as a whole and society, whereas the substantial increases in costs show up in the transfusion service budget. At 5 years from implementation, a new hospital administrator may ask why the blood bank budget has gone up by half a million dollars, and the justification may have to be gone through once again. In a sequential cohort study of costs, costs for leukoreduction and use of ABO identical transfusions in acute leukemia treatment ($875 per patient) or stem cell transplant for lymphoma ($643) were far exceeded by reductions in hospital charges for ancillary services ($14 000 for leukemia and $26 000 for lymphoma).[26] Length of stay and total use of blood components were also significantly reduced by more than enough to cover the costs of leukoreduction several times over. Whether the costs of washing transfusions leads to a net savings or expense is not known, but based upon unpublished cost data from our published randomized trial in induction therapy for acute leukemia[24] it appears that there were no significant differences in total hospital costs between those patients receiving ABO identical, leukoreduced transfusions and those receiving ABO identical, leukoreduced, washed transfusions. That is, that any additional costs of washing were offset by savings in resource consumption or too small to be detected.

Current clinical transfusion practice completely or partially disregards any risks of transfusing nonidentical soluble antigen (eg, infusing AB fresh frozen plasma into O, A, or B recipients), or antibody (O platelet concentrates into non-O recipients). Data from three groups[16,17,19,20,28–32] of clinical investigators have raised the question of whether current clinical practices may have unforeseen deleterious consequences to stem cell transplant patients. We would propose for debate that we should not infuse substantial amounts of anti-A and/or anti-B into patients whose peripheral blood or tissue cells express those antigens, nor should we be infusing substantial amounts of soluble or cell associated A and/or B antigen into those with measurable levels of the corresponding antibody (Tables 3 and 4).

This suggested new approach would require some inconvenience and expense, in the form of plasma removal or washing of cellular components, and some increased outdating of components. Our experience in the setting of acute leukemia and stem cell transplantation has been that use of ABO identical, leukoreduced transfusions is associated with reduced costs and morbidity[26,67] Further investigation is needed before we would advocate our practices be adopted as superior to the existing approach as there are significant resource, cost, and logistic consequences to blood transfusion services to do so. On the other hand, if immune complexes were to be demonstrated to interfere with platelet function, promote inflammation, predispose to TRALI, or immunomodulation, as seems probable, avoiding ABO nonidentical transfusions could reduce treatment-related morbidity and mortality in some proportion of stem cell transplant recipients. We are currently studying experimental models of the effects of ABO immune complexes on platelet function and inflammation to determine if the clinical observations we and others have made lend themselves to mechanistic investigation.

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